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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,382	03/14/2001	Benjamin Ethan Reubinoff	14418	1139
7590 SCULLY, SCOTT, MURPHY & PRESSER 400 Garden City Plaza Garden City, NY 11530			EXAMINER TON, THAIAN N	
		ART UNIT 1632	PAPER NUMBER	
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
3 MONTHS	12/29/2006	PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)
	09/808,382	REUBINOFF ET AL.
	Examiner Thaian N. Ton	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 28 September 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 39, 44-46, 51, 56-58, 60, 61, 63, 64, 67, 68, 86, 94 and 100-104 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 39, 44-46, 51, 56-58, 60, 61, 63, 64, 67, 68, 86, 94, 100-104 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

Applicants' Remarks, filed 9/28/06, have been considered entered. Applicants have presented no claim amendments with these remarks, thus, as previously, claims 39, 44-46, 51, 56-58, 60, 61, 63, 64, 67, 68, 86, 94, 100-104 are pending and under current examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* in view of Brustle. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 6/1/06 and 11/21/05.

Applicants' Arguments. Applicants argue that the claimed subject matter is not rendered obvious because 1) the prior art does not suggest the combination to one of ordinary skill in the art, and that 2) that the prior art does not reveal that one of skill in the art would have a reasonable expectation of success in carrying out the claimed invention. See page 2 of the Response.

Thomson Reference. In the prior Office action, the Examiner noted that the Thomson does not show that hES cells can differentiate to produce ectodermal cells *in vitro*, and further, that *in vivo*, ES cells could form teratomas containing ectodermal cells. Thus, the Examiner concludes that hES cells have the capacity to form neural cells of the ectodermal lineage given appropriate conditions. See pages 2-3, bridging ¶. Applicants argue that there has been no *in vitro* demonstration of

ectodermal cells being formed that could differentiate and eventually give rise to neuronal cells, and that the only conditions that are described by Thomson, in which hES cells can differentiate into cells of the ectodermal lineage are *in vivo* conditions. Applicants argue that Thomson does not teach or remotely suggest any *in vitro* conditions under which hES cells can differentiate into cells of the ectodermal lineage. Applicants argue that Thomson casts doubt with respect to the capacity of hES cells to differentiate, *in vitro*, into cells of the ectodermal lineage. Applicants argue that Thomson only demonstrates the differentiation of ES cells into derivatives of all three germ layers *in vivo*, in the teratoma example, and that given the contrast in the Thomson reference between the *in vivo* and *in vitro* differentiation results, one of skill in the art would conclude that it would be difficult to direct differentiation of hES cells towards the neural lineage *in vitro*. Applicants argue that given the showing that no ectodermal cells are formed *in vitro*, Applicants argue that Thomson would not have provided the requisite motivation for those skilled in the art to obtain NPCs *in vitro*, and that in fact, the reference could have discouraged those of skill in the art to attempt to obtain NPCs *in vitro* from hES cells. See pages 3-4 of the Response.

Response. These arguments are fully considered, but not persuasive. Thomson provides art that teaches the specific, essential characteristics of primate ES cells, including that they have “stable developmental potential to form derivatives of all three embryonic germ layers” (see page 1145, 1st col.). That is, for a cell to be considered an embryonic stem cell, it must be able to produce cells from all derivatives of all three embryonic germ layers. Clearly, the cells of Thomson are considered embryonic stem cells because they can produce cells from all three embryonic germ layers. If Thomson’s cells could not do this, they would not be considered pluripotent, embryonic stem cells. It is reiterated that Thomson provide *in vitro*, *spontaneously* differentiating conditions for their ES cells, which are not directed differentiation conditions, as instantly required. See page 1146, 1st col., 2nd

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full ¶. In conditions of spontaneous differentiation, and there is no control over which (if any) growth factors are introduced to the ES cells. The *in vivo* results of Thomson are used to show that their hES cells have the capability to form ectoderm lineage cells. Thus, the ordinarily skilled artisan would recognize that hES cells, such as those taught by Thomson, have specific characteristics that define them, including the ability to differentiate into cells that form all three embryonic germ layers. One of skill in the art would also recognize that a spontaneously differentiating condition (where the cells are simply allowed grow to confluence and pile up in the culture dish) is significantly different than a directed differentiation protocol, which requires specific growth factors, in order to specifically differentiate a population of cells. Further, Thomson even suggest the application of directed differentiation conditions, as taught in mouse ES cells, to hES cells, stating that, “[P]rogress has already been made in the *in vitro* differentiation of mouse ES cells to neurons, hematopoietic cells, and cardiac muscle. Progress in basic developmental biology is now extremely rapid; human ES cells will link this progress even more closely to the prevention and treatment of human disease.” See page 1147, 1st col., last sentence. Finally, it is reiterated that Thomson is not relied upon to produce the NPCs, and that Brustle provides the necessary steps and conditions to produce NPCs. Thomson provides sufficient evidence to show that human ES cells have the intrinsic ability to form ectodermal, and subsequently, neural lineage cells.

Brustle. Applicants argue that Brustle's techniques are directed to culturing mouse ES cells, and that the differences between mES cells and hES cells were so substantial, that those skilled in the art would not have had a reasonable expectation of success in applying the conditions developed using mES cells, taught by Brustle, to human ES cells, in order to obtain NPCs. Applicants argue that the Brustle reference only teaches the derivation of glial precursors, which can differentiate to oligodendrocytes and astrocytes only, and that this reference fails to

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teach the production of multipotential NPCs that can additionally give rise to neurons. See pages 4·5, bridging ¶ of the Response. Applicants argue further that that because the instant methods are directed to producing NPCs from human ES cells, whereas Brustle teaches methods relating to mouse ES cells, the source of cells is certainly part of the claimed methods, and thus, the Examiner's contention that there are no differences between the reference and the claimed methods fail on this ground alone. Furthermore, Applicants argue that the results in Brustle contradict the Examiner's arguments, namely that under the culture conditions taught by Brustle, mouse ES cells did not produce neuronal cells, and that it is unclear how using Brustle's methods, human ES cells would necessarily produce the NPCs (which additionally require the production of neurons), as instantly claimed. Applicants conclude that because the Brustle reference is entirely directed to mouse ES cells, there is no suggestion in this reference that would have motivated one of skill in the art to apply those conditions to human ES cells to produce the instantly-claimed NPCs. See pages 5·6 of the Response.

Response. These arguments have been fully considered, but are not persuasive. Firstly, it is reiterated that Applicants' methods have the exact same factors as that of Brustle. That is, Applicants have applied a mouse ES cell protocol to human ES cells. Both would have been obvious and readily available to the skilled artisan. Thus, if Applicants' method, when applied to human ES cells produce NPCs that can produce neurons, oligodendrocytes, and astrocytes, then, using these same factors and conditions (as taught by Brustle) on human ES cells (as taught by Thomson) would necessarily arrive at the NPCs that are capable of this differentiation. Secondly, in a careful review of Brustle, the Examiner notes that Brustle is silent on the presence or absence of neurons; thus, commenting on the ability of the neural progenitor cells to form neurons is mere speculation, absent specific evidence. Brustle discusses testing the cells using a monoclonal antibody, A2B5, which recognizes glial precursors, and that the cells, upon growth factor

withdrawal differentiated into oligodendrocytes and astrocytes (p. 754, col. 2). However, Brustle does not comment upon any presence or absence of neurons. The claims do not require a specific yield or percentage of cells, and thus, the generation of a single NPC that can generate neurons is sufficient to fulfill the claims. Accordingly, it is maintained that Brustle provide sufficient motivation to arrive at the claimed invention, in that they provide methods that generate neural precursor cells from embryonic stem cells.

Reasonable Expectation of Success. Applicants argue that there is a lack of reasonable expectation of success, to culture the hES cells of Thomson, under the conditions taught by Brustle, to arrive at the claimed invention. Applicants argue that it was evident at the relevant time, the differences between mouse and human ES cells, such that one of skill in the art would not have had a reasonable expectation of success that hES cells would have behaved in the same manner as mES cells. Applicants further argue that the Colman Declaration (provided in the previous Response) showed the distinctions between mES and hES cells in Table 1, and that the Declaration also referenced various supporting articles that addressed the distinctions between mES and hES cells. Applicants argue that Xu *et al.* (cited previously) reported the induction of differentiation of hES cells to trophoblast using the growth factor BMP4, whereas mES cells cannot form trophoblasts. Applicants argue that the Examiner stated that the Xu reference referred to Beddington, which only describes *in vivo* tests of mES cells, and does not provide any comparison of mES cells with hES cells under *in vitro* conditions. Applicants argue that the Examiner is inconsistent because the Examiner has previously relied upon the teachings of Thomson with regard to the *in vivo* behavior of hES cells. See pages 6-7 of the Response.

Niwa. Application argue that they provide Niwa *et al.* which describes that mES cells were converted by genetic engineering into cells capable of making trophoblasts, and that the need for such a radical approach is consistent with the

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notion that unlike human ES cells, it is very difficult, if not impossible to direct mES cells to differentiate to trophoblast cells in culture via a non-genetic engineering approach. Applicants argue further that Niwa provide differences between mES and hES cells. See page 7, 3rd ¶ of the Response.

Response. Applicants' arguments have been fully considered, but are not persuasive. The Examiner is not inconsistent with regard to Xu's and Beddington's *in vivo* results. In particular, the Examiner has used the teratoma formation, as taught by Thomson to show that human ES cells can form cells of ectodermal lineage. The Examiner does not rely upon Thomson with regard to directed differentiation. Similarly, Xu teaches that mouse ES cells yield very low numbers of trophoblast cells (not that mES cells are unable to form any trophoblast cells). Furthermore, the Examiner notes that the formation of trophoblasts cells are not within the scope of the claimed invention. In particular, the Examiner directs Applicants' attention to Thomson, who provide the specific definition for characteristics of ES cells, particularly, that they are *pluripotent* cells that are capable of forming cells from all three embryonic germ layers (*i.e.*, endoderm, ectoderm and mesoderm). This definition is also supported by the NIH's Stem Cells Scientific Progress and Future Research Directions, Appendix F.i. (Glossary and Terms), pages F-1-F-12, 2001, who provide definitions for the term "pluripotent stem cell" (see page F-8, 2nd col), as, "A single stem cell that has the capability of developing cells of all germ layers (endoderm, ectoderm, and mesoderm)." The NIH definition for "totipotent" reads as follows: "Having unlimited capability. The totipotent cells of a very early embryo have the capacity to differentiate into extraembryonic membranes and tissues, the embryo, and all postembryonic tissues and organs." See page F-10, 1st col., *emphasis added*. The Examiner further provides The definition of a trophoblast (<http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=trophoblast>, accessed online, December 21, 2006) as, "Extra embryonic layer of epithelium that forms around the mammalian blastocyst and

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attaches the embryo to the uterus wall.” Thus, trophoblast cells, as clearly shown by these definitions, are cells that are part of extra embryonic tissues and are not considered part of the embryo proper. In fact, it is clear from these definitions, that pluripotent stem cell (such as hES cells) can form cells from the three germ layers, in order to be considered pluripotent. Accordingly, Applicants’ arguments, with regard to the formation of trophoblast cells (which are extra embryonic tissues) from mES cells is not considered analogous to the instant invention, which are directed to differentiation of pluripotent cells.

Reubinoff. Applicants argue that mES cells and hES cells behave differently, as evidenced by an article published in *Nature Biotechnology* (Reubinoff *et al.*), where the authors report that conditions that were used to facilitate formation of embryoid bodies (EBs) from mES cells did not result in the formation of EBs from human ES cells. See pages 7-8 of the Response.

Response. The Reubinoff paper has been considered, but not found to be persuasive. This paper was published within one month of Applicants’ earliest priority date, and thus, represents art at the time of filing. In this paper, Reubinoff *et al.* state that they confirmed the results of Thomson, with regard to the derivation of human ES cell lines from human blastocysts, and that the show that human ES cells can produce neural progenitor cells from ES cell cultures. See page 399, 2nd col., 1st ¶. Thus, this paper provides evidence that Thomson’s ES cells were recognized by those of skill in the art, at the time of filing, as ES cells, (*i.e.*, that they had the specific characteristics of ES cells with regard to their ability to differentiate, be maintained in an undifferentiated state, and express specific markers, see pages 399-400) and that hES cells are capable of producing neural progenitor cells *in vitro*. This paper further teaches that although EBs were not able to be generated using standard techniques, they teach that, “Nevertheless, somatic differentiation could be established under conditions such as prolonged cultivation.” See page 401, 2nd col., 1st paragraph. Furthermore, they teach the

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isolation and differentiation of neuronal progenitor cells from hES cell cultures (pages 401-402, bridging ¶). Accordingly, the Reubinoff paper provides evidence that at the time of filing, those of skill in the art would recognize the ability of hES cells to form neural progenitor cells, and that this paper further supports Thomson's determination that the cells are indeed pluripotent.

Colman Declaration. With regard to gp130 deficiency, Applicants argue that the Colman Declaration was not intended to show that hES cells cannot form cells of neuronal lineages due to the gp130 deficiency; rather, Applicants intended to establish that the prior art at the relevant time cast doubt on the likelihood of success in attempting to derive NPCs from human ES cells applying protocols developed with mouse ES cells. Applicants argue that they do not need to show that the art at the relevant time indicated to those of skill in the art that it was impossible to arrive at the claimed invention. See page 8 of the Response.

Response. Applicants' arguments have been fully considered, but are not persuasive. In particular, the Examiner is not arguing that Applicants must show that it would be impossible to arrive at the claimed invention. Rather, the Examiner has provided sufficient evidence to show that Thomson's cells have the capability to produce ectodermal lineage cells, as evidenced by their formation of these lineage cells in teratoma formation. It is further reiterated that directed differentiation techniques are far different than spontaneous differentiation. The comparison of spontaneous differentiation technique with directed differentiation techniques are not analogous. As such, the Examiner maintains that Thomson's teachings of cells that have the capability to form neural lineage cells, does not suggest that it would be difficult to produce neural lineage cells, as Thomson is silent with regard to specific, directed differentiation conditions. Furthermore, Thomson do suggest using mouse ES cell protocol with human ES cells, stating that, "[P]rogress has already been made in the *in vitro* differentiation of mouse ES cells to neurons, hematopoietic cells, and cardiac muscle. Progress in basic

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developmental biology is now extremely rapid; human ES cells will link this progress even more closely to the prevention and treatment of human disease.” See page 1147, 1st col., last sentence. Because Applicants have provided no nexus between the gp130 deficiency and the ability of hES cells to form neural lineages (which, as evidenced by Thomson, and also provided by Applicants’ in the Reubinoff paper, show that hES cells can and do form neural lineages), this argument is not found to be persuasive.

Applicants’ Arguments. Applicants argue that the Examiner’s reliance on the Thomson reference, which merely shows the potential of hES cells to differentiate into ectodermal cells *in vivo* in the teratoma example. Applicants argue that there is no teaching or suggestion in the Thomson reference that human ES cells would have capacity to differentiate into ectodermal cells *in vitro*, and that in fact, the *in vitro* results of Thomson would have suggested that it would be difficult to direct differentiation of hES cells towards the neural lineage *in vitro*. Applicants argue that there is no reasonable expectation of success in arriving at the claimed invention, because Thomson’s cells did not produce ectodermal cells *in vitro*, and thus, the combination of the Thomson and Brustle references fail to provide those of skill in the art a reasonable expectation of success in producing human NPCs *in vitro* by applying the conditions developed with mouse ES cells. Applicants further argue that as of the priority date of the present invention, human ES cell research was still in its infancy, and that conditions for culturing and differentiation were more established for mouse ES as compared to human ES cell, and that the art at the time of filing reflects the uncertainties and difficulties associated with deriving differentiated cells from hES cells. Applicants cite the Thomson patent, which provides differences between human and mouse embryos, and that analogous experiments on primate ES cells demonstrate that EB formation by conventional murine protocols failed, and that a need for improved method for producing EB and differentiated cells therefrom exists. Applicants argue that thus, the Thomson

patent suggests that deriving differentiated cells from hES cells, based upon a method involving EB formation, which Brustle also rely upon, would not have had a reasonable expectation of success. See pages 8-10 of the Response. Applicants conclude that neither Thomson nor Brustle would have provided motivation to combine the respective teachings and apply the conditions, taught by Brustle, to human ES cells, in order to produce human NPCs. Furthermore, Applicants argue that there is no reasonable expectation of success in applying the conditions taught by Brustle, to human ES cells to produce human NPCs, much less to produce human NPCs with the multipotent differentiation capacity, as presently claimed. See pages 10-11 of the Response.

Response to Arguments. Applicants' arguments are considered, but not found to be persuasive. In particular, Applicants' arguments are not analogous with the claimed invention. The claimed invention is directed to the directed differentiation of hES cells to neural progenitor cells, under specific conditions, with specific media and growth factors. Thomson *et al.* teach that in spontaneously differentiating conditions, hES cells did not form ectoderm lineage cells. However, they do show that the hES cells have the capability to do so, as shown by the formation of teratoma *in vivo* results, under appropriate conditions. Thus, although spontaneous differentiation does not result in ectoderm formation, this does not mean that hES cells cannot form ectoderm lineage cells. This is clearly show by Thomson's results showing ectodermal cells in teratomas formed when hES cells are injected into SCID mice. Teratoma formation is routinely used in the art to show the differentiation potential of an ES cell. Since Thomson *et al.* showed hES cells form ectodermal cells in a teratoma, and ectodermal cells give rise to neural progenitor cells, as taught by Brustle, the artisan would have had the teachings, suggestion and motivation to apply the differentiation method, taught by Brustle, which target the differentiation of mES cells, which form ectodermal cells in a teratoma, using culture conditions identical to those claimed. One of skill in the art would have had

a reasonable expectation of success, because hES cells, as mES cells, formed ectodermal cells in a teratoma.

In short, one of skill in the art, at the time of filing, would have recognized differences between hES cells and mES cells, particularly with regard to culturing the cells in presence of LIF. However, one of skill in the art would have also recognized that hES cells had the capacity to differentiate into cell types from all three embryonic germ layers, including cells of neuronal lineage (as taught by Thomson). One of skill in the art would recognize that protocol existed to direct differentiation of mouse ES cells to a particular cell type (such as neuronal cells) (as taught by Brustle). The claims do not require a particular yield or amount of cells to be produced, thus, one of skill would have a reasonable expectation, given the combined teachings, to produce at least one NPC that would be capable of differentiation to cells of neurons, oligodendrocytes, and astrocytes. One of skill in the art would be motivated to use this protocol on human ES cells, with a reasonable expectation of success. Accordingly, the prior rejection is maintained.

Claims 58-58, 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* in view of Brustle *et al.* as applied to claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 above, and further in view of Stemple *et al.* This rejection is maintained for reasons of record, advanced in the prior Office actions, mailed 6/1/06 and 11/21/05.

Applicants' present no specific arguments with regard to this rejection. Applicants' arguments are addressed above. It is maintained that, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells, as taught by Thomson, in serum free media in the presence of FGF2 and PDGF-AA on polyornithine to form neural precursors, as taught by Brustle, but growing in the precursors in a media comprising retinoic acid and growth on poly-D-lysine and laminin coated plates to induce neuronal growth, as

taught by Stemple, for drug discovery and/or transplantation therapies. The methods will necessarily result in neural progenitor cells that express the particular markers claimed, because the claims require the same growth factors and medium. The cited prior art provides sufficient suggestion, teaching and motivation to arrive at the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 61, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson in view of Brustle in view of Stemple, as applied to claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 above, and further in view of Ben-Hur. This rejection is maintained for reasons of record, advanced in the prior Office actions, mailed 6/1/06 and 11/21/05.

Applicants' present no specific arguments with regard to this rejection. Applicants' arguments are addressed above. Thus, it is maintained that it would have been obvious for one of ordinary skill in the art, at the time of filing, to culture the human ES cells, as taught by Thomson in serum free media in the presence of FGF and PDGF-AA, on polyornithine to form glial precursors and then, in the absence of growth factors, to form predominantly oligodendrocytes and astrocytes, as taught by Brustle, but growing the precursors on poly-D-lysine and fibronectin coated plates, in order to enhance the presence of neurons in the differentiated cells and in the presence of EGF to enhance neuron differentiation, followed by culture with EGF and T3 to produce a culture of neuronal cells, oligodendrocytes, and glia cells for drug discovery and/or transplantation therapies, as taught by Ben-Hur, with a reasonable expectation of success.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

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Claims 68 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson and Brustle as applied to claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 above, and further in view of Ben-Hur. This rejection is maintained for reasons of record, advanced in the prior Office actions, mailed 6/1/06 and 11/21/05.

Applicants' present no specific arguments with regard to this rejection. Applicants' arguments are addressed above. Accordingly, it is maintained that, at the time of the claimed invention, it would have been obvious for one of ordinary skill in the art, to produce oligodendrocytes by culturing the human ES cells, as taught by Thomson in DMEM/F12 media, in the presence of FGF2 and EGF to form glial precursors, as taught by Brustle, and to further culture the glia cells in the presence of B27, FGF2 and EGF, as taught by Ben-Hur, in combinations to provide oligodendrocytes for drug discovery and/or transplantation. The cited art provides sufficient suggestion, teaching and motivation to achieve the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

thaian ton
THAIAN N. TON
PATENT EXAMINER